A Comparison of Trends in the Incidence of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma in the United States

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Abstract

The incidence rates of liver cancers, both hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC), are increasing in the U.S. It is possible that the increases are related to common exposures, and if so, similar trends in incidence by gender, age, ethnicity, and calendar period, might exist. To examine this hypothesis, age-specific trends in the incidence of HCC and ICC in the Surveillance, Epidemiology and End Results program (1976-2000) were examined by year of diagnosis and year of birth. Age-period-cohort models were also fit to the data. The incidence of HCC in the most recent time period was twice as high among Black men (8.8/100,000) and women (2.6/100,000) as among White men (4.6/100,000) and women (1.2/100,000). However, between 1976 and 2000, incidence among all four ethnic- and gender-specific groups increased by >90% (White males, 123.2%; White females, 96.8%; Black males, 97.9%; Black females, 91.9%) with young White men experiencing the greatest increases (432%). In contrast, ICC rates were similar for Black (0.93/100,000) and White men (0.92/100,000), but higher for White (0.57/100,000) than Black women (0.39/100,000). Although ICC incidence increased among all groups, the increase was greatest for Black men (138.5%), followed by White men (124.4%), White women (111.1%), and Black women (85.7%) Age-period-cohort analyses of HCC revealed a significant cohort effect among younger men (45-65 years old), but not older men (65-84 years old), suggesting possible differences in etiology. In conclusion, the rates of HCC and ICC approximately doubled between 1976 and 2000. Trends by age, gender, ethnicity, and birth cohort suggest that heterogeneity exists in the factors influencing these rates. (Cancer Epidemiol Biomarkers Prev 2006;15(6):1198–203)

Introduction

Primary liver cancer (PLC) incidence rates have been rising in many developed countries, including the U.S. (1). Both major types of liver cancer, hepatocellular carcinoma (HCC), with an overall incidence rate of 2.99 per 100,000, and intrahepatic cholangiocarcinoma (ICC), with an overall incidence rate of 0.71 per 100,000, have experienced increases in incidence in the last quarter-century (2, 3). Even though HCC, which accounts for 65% of liver cancer in the U.S., is twice as common among Black Americans as White Americans, the largest increases have been reported to be experienced by White men (4). In contrast, the rates of ICC, which account for 14% of liver cancers, do not vary as greatly by sex and race (5).

The causes of the increases in incidence of liver tumors are not well understood, although it has been widely speculated that hepatitis C virus (HCV) is responsible for the increases in HCC. With some minor exceptions, the risk factors for the two cancers have seemed to be distinct (6). The most significant risk factors for HCC in the U.S. are cirrhosis, HCV infection, and alcohol consumption, whereas the only well-identified ICC risk factor is primary sclerosing cholangitis, with or without concomitant inflammatory bowel disease (6, 7). Some recent evidence suggests, however, that HCV, particularly in conjunction with alcohol, may also be related to ICC (8-17). If HCV, or other common factors, are jointly responsible for the increases in HCC and ICC, the age-sex-ethnic incidence patterns of the tumors may show parallel patterns. To determine whether this was true for HCC and ICC in the U.S., we examined incidence rates in the Surveillance, Epidemiology, and End Results (SEER) program over the time interval between 1976 and 2000. We also compared the tumors using age-period-cohort models to assess whether similar patterns existed.

Materials and Methods

Incidence data for HCC and ICC were obtained from the SEER Program, a population-based cancer registry system in certain areas of the U.S. (18). Data from nine registries that have been part of SEER since 1975 or earlier were included. These registries represent the states of Connecticut, Hawaii, Iowa, New Mexico, Utah, and the metropolitan areas of Atlanta, Detroit, San Francisco-Oakland, and Seattle-Puget Sound. HCCs were identified by site code C22, behavior code malignant, and ICD-O-2 histology codes 8170 and 8171, whereas ICCs were identified by site code C22, behavior code malignant, and ICD-O-2 histology codes 8160, 8260, 8481, 8500, and 8560. PLCs of poorly specified morphology (i.e., morphology codes <8140) were not included. Similarly, PLCs of well-specified morphology that were not either HCC or ICC were not included (i.e., all morphology codes other than those listed previously). The SEER*Stat statistical software package was used to calculate incidence rates, which were age-adjusted to the U.S. standard population of 2000. To examine age-specific trends by year of diagnosis and year of birth, rates were calculated for 5-year age groups and 5-year time periods. Rates were plotted by calendar year of diagnosis and calendar year of birth using a logarithmic scale for the ordinate (19).

To examine age, calendar period, and birth cohort effects simultaneously, age-period-cohort models were fit by Poisson regression to the HCC and ICC incidence data by use of 5-year age and calendar period intervals (20, 21). For both tumors,

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there were eight age intervals (45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, and 80-84 years), five calendar period intervals (1976-1980, 1981-1985, 1986-1990, 1991-1995, and 1996-2000), and 12 birth-year intervals (1891-1900, 1896-1905, 1901-1910, 1906-1915, 1911-1920, 1916-1925, 1921-1930, 1926-1935, 1931-1940, 1936-1945, 1941-1950, and 1946-1955). In the text and figures, each birth cohort is identified by the 5th year in the interval. For example, the 1895 birth cohort refers to persons born between 1891 and 1900. The final birth cohort is not plotted in the figures because it is based on a single comparison of rates in the youngest age groups and, as a result, could be extremely unstable. Due to the relatively small number of ICCs among Black men and women, the ICC age-period-cohort analyses were only modeled on rates from White men and women.

The interpretation of individual variable estimates from age-period-cohort analyses can be difficult because variables are not identifiable (i.e., there is no unique set of estimates; refs. 20, 21). The first step in the analysis was to fit a model specifying a linear (on the logarithmic scale) increase in incidence rates (i.e., the drift model; ref. 20). If the drift model adequately describes the trend in incidence rates, then no further exploration of trends is warranted (20). If the drift model does not adequately describe the incidence trends, then a full age-period-cohort analysis is required to document important nonlinear patterns of risk (i.e., either calendar period patterns or birth cohort patterns of risk; refs. 20, 21). A change in the slope of the birth cohort effects curve or the calendar period effects curve is identifiable; that is, such a change does indicate an actual variation in the disease rate trend (21). An increase (or decrease) in the slope of the birth cohort effects indicates a worsening (or moderation) in the birth cohort pattern of risk. Such a change usually reflects a change in exposure to an etiologic factor or factors. Changes in the slope of the lung cancer birth cohort effects curve, for example, reflect changes in the prevalence of cigarette smoking (22). An increase (or decrease) in the slope of the calendar period effect curve indicates a worsening (or moderation) in the incidence trend simultaneously in all (or most) age groups around the same calendar year. Such changes for cancer incidence rates usually reflect changes in diagnostic methods or changes in disease classification (i.e., coding changes), although they can also reflect changes in exposure to an etiologic factor (e.g., hormone replacement therapy and endometrial cancer; ref. 23).

Results

Incidence rates of all types of PLC increased during the period of interest (Table 1). Rates of HCC (up 123.1%) and ICC (up 121.9%), however, increased more than the rates of other liver cancers. The bases of diagnostic confirmation of HCC and ICC also changed throughout the period, with proportionally fewer tumors being confirmed microscopically and more tumors being confirmed by other methods, particularly radiography (Table 2).

Age-Adjusted Trends in HCC and ICC. HCC rates for Black men and women were consistently higher than corresponding HCC rates for White men and women, respectively (Fig. 1A). In the most recent time period, 1996 to 2000, Black males had an HCC incidence rate almost twice that of White males (8.8/100,000 versus 4.6/100,000). Similarly, the Black female rate was twice as high as the White female rate (2.6/100,000 versus 1.2/100,000). HCC rates, however, increased by ~100% in all four groups (White males, +123.2%; Black males, +97.9%; White females, +96.8%; Black females, +91.0%) between 1976 to 1980 and 1996 to 2000.

In contrast to the clear excess of HCC among Black individuals, White and Black men had very similar annual incidence rates of ICC (e.g., in the 1996-2000 period, White males, 0.92/100,000; Black males, 0.93/100,000; Fig. 1B). Furthermore, White women had an incidence rate almost 50% higher than Black women (e.g., in 1996-2000, White females, 0.57/100,000; Black females, 0.39/100,000). Between 1976 to 1980 and 1996 to 2000, ICC rates approximately doubled in all four gender- and ethnic-specific groups. Three of the four groups, White women, Black men, and Black women, experienced a rather large increase (61.5%, 151.6%, and 84.2%, respectively) in the interval between 1981 to 1985 and 1986 to 1990. Such an increase was not observed in White men. The greatest increase in White male rates, +33.3%, occurred 5 years later, between 1986 to 1990 and 1991 to 1995.

Age-Specific Trends in HCC and ICC. Figure 2A shows the age-specific HCC incidence rates for the 1996 to 2000 calendar period. The HCC incidence curves of all four groups tended to increase rapidly at the younger ages, but to level off, and even decline, at the older ages. Among White men and women, the curves plateaued at age >70. Among Black men, however, the curves leveled off much earlier, at age >55. In fact, starting at age 70, there is little distinction between the rates of Black and White men. There was no clear plateau in the curve for Black women prior to the downturn in incidence among the oldest group. The highest incidence of HCC occurred at ages 75 to 79 among both Black and White males. Among females of both ethnic groups, the peak age of incidence occurred among the 80- to 84-year-old group.

Figure 2B shows the age-specific ICC incidence rates for the 1996 to 2000 calendar period. Unlike the HCC incidence curves, the ICC incidence curves show little or no evidence of leveling off at older ages. All four curves are consistent with a linear increase (on the logarithmic scale) with increasing age. Among all four sex- and ethnic-specific groups, the age-specific rates of ICC were highest in the oldest age group (85+ years). In this age group in the most recent time period, the rate among White males was 8.7 per 100,000, whereas the rate among Black males was 9.9 per 100,000. Among White females, the rate was 5.9 per 100,000, whereas among Black females, the rate was 3.7 per 100,000.

Age-Period-Cohort Analyses. The drift model, specifying a constant linear (on the logarithmic scale) increase in incidence rates, provided an adequate fit to the HCC rates for White women ($P = 0.41$) and Black women ($P = 0.75$). The slope estimates (and corresponding SEs) from the drift model were: White women, 0.19 ($\pm$0.017); Black women, 0.20 ($\pm$0.039). The drift model also provided an adequate fit to the ICC rates for both White women ($P = 0.36$) and White men ($P = 0.55$), with slope estimates and SEs of 0.21 ($\pm$0.023), and 0.19 ($\pm$0.025), respectively. Thus, for HCC in White and Black women and ICC in White women and men, the model specifying a steady increase of ~20% every 5 years provided an adequate fit to the incidence data. As these drift models adequately fit the data, no further exploration of trends was justified as it would be impossible to distinguish between a linear birth cohort increase and a linear calendar period increase (20).

Age-period-cohort modeling of HCC rates among men was more complex. Among White men, the drift model did not provide an adequate fit to the incidence rates ($P < 0.0001$). Even the full age-period-cohort model did not provide an adequate fit ($P = 0.0055$). Plots of the age-specific incidence rates in Fig. 3 indicate that older men (≥65 years) and younger men (<65 years) had different secular trends. In particular, there was an acceleration of the increase in rates for the younger men in the last calendar period, whereas there was a slight deceleration of the increase in rates for the older men. Because of apparent differences in trends, age-period-cohort analyses were done separately for men <65 years of age and for men ≥65 years of age. For younger men, although the drift

Table 1. Incidence and proportion of PLC among Black and White persons by morphologic type, SEER-9 registries (1976-2000)

	HCC	ICC	Poorly specified PLC	Other PLC	Total PLC
	Incidence (PLC %)	Incidence (PLC %)	Incidence (PLC %)	Incidence (PLC %)	Incidence
1976-1980	1.34 (57.4)	0.32 (13.8)	0.40 (15.1)	0.32 (13.8)	2.38
1981-1985	1.55 (60.9)	0.34 (12.9)	0.34 (12.8)	0.34 (13.4)	2.56
1986-1990	1.80 (60.8)	0.49 (16.0)	0.35 (11.1)	0.36 (12.1)	3.00
1991-1995	2.27 (61.0)	0.62 (16.3)	0.40 (10.5)	0.45 (12.2)	3.73
1996-2000	2.99 (63.4)	0.71 (15.1)	0.50 (10.6)	0.51 (10.9)	4.72
Increase	123.1%	121.9%	25.00%	59.4%	98.3%

NOTE: Incidence rate per 100,000 persons. SEER database (http://www.seer.cancer.gov). SEER*Stat Database: Incidence-SEER 9 Regs Public-Use, Nov 2002 Sub (1973-2000) [18 Age Groups], National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2003, based on the November 2002 submission. HCC morphology codes: 8170 to 8171. ICC morphology codes: 8160, 8260, 8481, 8500, and 8560. Poorly specified morphology codes: 8000 to 8130. Other PLC morphology codes: all other morphology codes.

model did not provide an adequate fit to the rates ($P < 0.0001$), the full age-period-cohort model did fit ($P = 0.89$). For older men, the drift model did not provide an adequate fit to the HCC rates ($P = 0.002$), and the full age-period-cohort model fit only marginally well ($P = 0.03$). Figure 4 shows the plot of the calendar period effects for men <65 years of age and for men aged ≥65 years. A notable feature of Fig. 4 is the large increase in slope of the younger men's line in the late 1990s. In contrast, the slope of the older men's line decreased slightly during the same interval. The increase in slope in younger men in the late 1990s was significant ($P = 0.0004$), and the change in slope was significantly greater in younger men than in older men ($P = 0.0013$). There was little evidence of any notable calendar period effects for the older men ($P = 0.19$). Plots of the cohort effects for the younger and older men are shown in Fig. 5. There was strong evidence for birth cohort variation of risk in young men ($P < 0.0001$), primarily due to an increase in the slope of the birth cohort risk curve around 1935 ($P < 0.0001$). There was marginal evidence for birth cohort variation in risk for older men ($P = 0.034$), probably reflecting the increase in the slope of the birth cohort risk curve around 1910.

As with the HCC rates of White men, the drift model did not provide an adequate fit to the HCC rates among Black men ($P = 0.0009$). Once again, the older and younger men had different patterns of risk. Among the older men (≥65 years of age), the drift model did provide an adequate fit to the data ($P = 0.23$), but the slope estimate was only 0.083 (±0.34). This estimate was considerably lower than the 0.20 slope observed for the other three gender/ethnic groups in HCC and the White rates for ICC. The drift model did not provide an adequate fit to the HCC rate of the younger Black men ($P = 0.009$), but the full age-period-cohort model did ($P = 0.15$). There was no evidence of significant calendar period variation in risk ($P = 0.38$), but there was a significant increase in the birth cohort slope in risk beginning with the birth cohort of 1935 ($P = 0.028$). The estimate of drift in the full age-period-cohort model for young Black men is 0.21 (±0.041).

Discussion

Although the incidence of cancer of all sites in the U.S. remained stable between the mid-1970s and 2000, the incidence rates of all types of liver cancer continued to climb (24). During the time period of interest, the proportion of liver cancer that was poorly specified had morphologically declined, suggesting that some of the increase in the proportion of liver cancer due to HCC and ICC may have been due to better diagnosis. It should be noted, however, that the rates of all types of liver cancer (including liver cancers of poorly specified morphology) increased, suggesting that diagnostic shift wasn't the only possible explanation for increasing rates of HCC and ICC. Speculation about the role of HCV in HCC incidence has been prominently discussed (4). Comparisons with HCC increases in Japan, which are known to be HCV-related, have suggested that the U.S. might experience a similar epidemic in the near future (25). As several reports have noted associations between HCV and ICC, similar HCV-related increases in ICC might also be anticipated (8-17). In the current report, we examined age-specific and temporal trends in the rates of HCC and ICC to

Table 2. Diagnostic confirmation of HCC and ICC by year groupings, SEER-9 registries (1976-2000)

	Microscopically confirmed (%)	Positive laboratory test/ marker study (%)	Direct visualization without microscopic confirmation (%)	Radiography without microscopic confirm (%)	Clinical diagnosis only (%)	Unknown (%)
HCC*						
1976-1980	92.5	0.0	0.3	4.7	0.7	1.8
1981-1985	87.1	0.0	0.6	8.4	2.1	1.8
1986-1990	86.9	0.7	0.3	7.9	2.0	2.2
1991-1995	81.9	2.1	0.2	10.6	2.6	2.5
1996-2000	79.3	2.9	0.2	12.5	1.9	3.2
ICC†						
1976-1980	92.4	0.0	2.2	4.0	0.4	1.1
1981-1985	77.8	0.0	5.0	13.9	3.0	0.3
1986-1990	66.7	0.0	6.0	22.1	3.2	1.9
1991-1995	67.1	0.0	4.1	19.2	7.1	2.5
1996-2000	72.4	0.0	3.9	16.2	3.4	3.9

NOTE: SEER database (http://www.seer.cancer.gov) SEER*Stat Database: Incidence-SEER 9 Regs Public-Use, Nov 2002 Sub (1973-2000) [18 Age Groups], National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2003, based on the November 2002 submission.
*Morphology codes: 8170-8171.
†Morphology codes: 8160, 8260, 8481, 8500, and 8560.

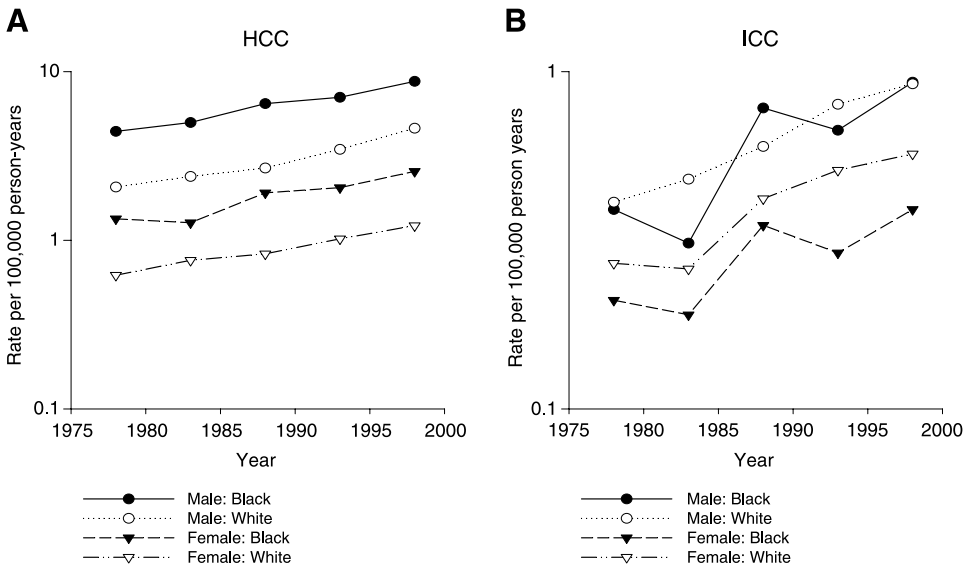

Figure 1. Age-standardized incidence rates of (**A**) HCC and (**B**) ICC by ethnicity and gender (SEER, 1976-1980 to 1996-2000). Rates standardized to the 2000 U.S. population.

see whether they suggested that a common factor, be it HCV or other exposure, was affecting the rates of both liver tumors.

Overall, the secular trends of the two tumors show some similarities. The incidence of both tumors approximately doubled between 1976 and 2000, and the drift models of HCC among women and ICC among White men and women are consistent with log-linear increases in all age groups. These findings are not inconsistent with a common risk factor being associated with both tumors.

In contrast to the similarities, there are also some dissimilarities in the HCC and ICC trends. There are certainly ethnic and age differences in risk. Although there is a clear HCC excess among Black persons, there is a slight ICC excess among White persons (i.e., White women). In terms of age, the risk of HCC levels off and even declines with age, whereas the risk of ICC increases steadily. In addition, the pattern of HCC risk among younger men is distinct from ICC risk among younger men and distinct from HCC risk among women of all ages. These observations suggest that different risk factors could be responsible for the varying patterns in HCC and ICC. Alternatively, the same factor could be related to both tumors but pose a much greater risk for one than the other. If the latter hypothesis is correct, the data also suggest that the timing of the exposure to the factor may vary by subgroup.

One factor that has been the subject of much investigation is HCV. It is speculated that HCV became more common in the U.S. population in the 1960s as a result of injection drug use (26). Based on back-extrapolation to the origins of the U.S. HCV epidemic, it has been estimated that the cohort of individuals born between 1940 and 1965 are the persons most likely to have been infected with HCV (26). The oldest of these individuals would have first moved into the 45- to 49-year-old age group in the late 1980s. Thus, the large increase in HCC incidence among males in the younger age groups in the 1990s is consistent with the timeline of the HCV epidemic. It is also consistent with the findings of our age-period-cohort analysis of both White and Black men, which found a cohort effect among men born in cohorts starting around 1935. In addition, data from both Japan and the U.S. indicate that the latency period between HCV infection and the development of HCC is

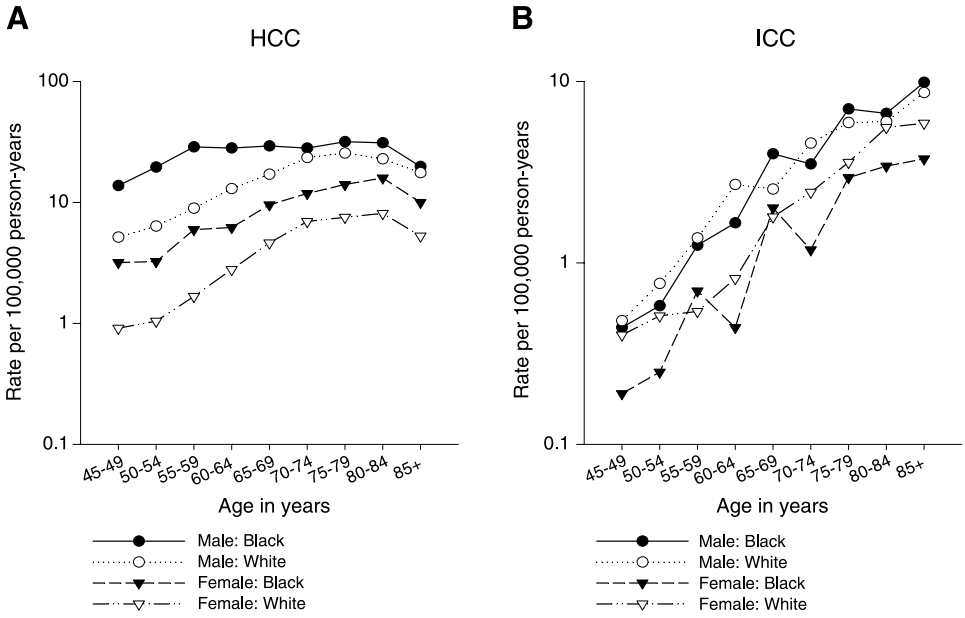

Figure 2. Age-specific incidence rates of (**A**) HCC and (**B**) ICC by ethnicity and gender (SEER, 1996-2000).

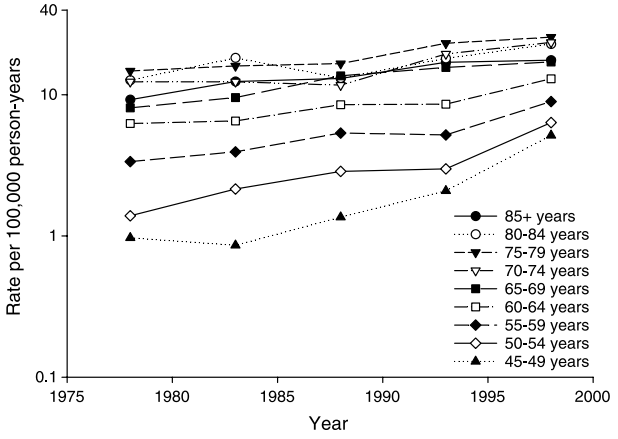

Figure 3. Age-specific incidence rates of HCC among White males by age-group (SEER, 1976-1980 to 1996-2000).

roughly 25 to 30 years, thus supporting a link between events of the 1960s and 1990s (27).

The difference in the male and female HCC patterns suggest that, if HCV is the main factor driving the HCC increase, females did not have the same exposure to HCV that males did in the 1960s. Data from the National Household Survey on Drug Abuse support this suggestion as the lifetime probability of females in the 1940 to 1965 birth cohorts ever using i.v. drugs is less than half the lifetime probability of the comparable males.[4]

If HCV infection from injection drug use explains the increase in HCC rates among the younger male population, the increased HCC rates among the older individuals still require an explanation. One possibility is that the lower increase in older persons may be related to HCV acquired through blood transfusion. HCV circulated in the nation's blood supply and acted as the major contributor to transfusion-associated hepatitis prior to 1970 (28). After 1970, better selection and screening of potential blood donors by a variety of means gradually contributed to eradicating HCV from the blood supply. Once HCV antibody screening became available in 1990, the U.S. blood supply was no longer a source of significant infection (28). In the 1970s and 1980s, the risk of transfusion-associated hepatitis was between 5% and 10% (28), and older persons were more likely to receive transfusions (29). The transfusion explanation is consistent with data from the Veterans Administration that found the largest increase in HCV-related HCC in the 1990s occurred among persons aged 45 to 60 years, whereas smaller increases in HCV-related HCC occurred among older persons (30). It is unclear, however, why the slower increase in risk of older Black men varied from the other three gender- and ethnic-specific groups. It is conceivable that the older Black men were less likely to receive blood transfusions than the other groups or, as is suggested by the age pattern of HCV rates in the National Health and Nutrition Examination Survey III population (26, 29), their exposure to HCV started at an earlier time point than the other groups.

Other explanations for the increase in HCC rates include better survival among cirrhotic patients, better diagnosis and possibly, increased rates of diabetes and obesity. Other well-known HCC risk factors, such as HBV infection, alcoholism, and hemochromatosis are unlikely to explain the increase as the rates of these exposures among Whites and Blacks have not appreciably increased.

The relationship between HCV and ICC has not been as extensively studied as the relationship between HCV and HCC. However, several case-series (8, 9, 31), case-control studies (15-17), and one cohort study (14) have reported a HCV-ICC relationship. In contrast, two case-series from Thailand reported no relationship (32, 33). Among the positive studies that have examined HCV in relationship to both HCC and ICC, the risk of HCC has been consistently shown to be greater than that of ICC (15, 31, 34). Collectively, the data indicate that an association between HCV and ICC may exist. Why the ICC age- and sex-specific patterns are not more similar to the HCC patterns is unclear. It is possible that HCV only increases the risk of ICC in the presence of other factors so that younger persons without other ICC risk factors would not be at increased risk even if they were infected with HCV.

In contrast to the positive reports of an association between HCV and ICC, there does not seem to be an association between HBV and ICC (8, 15, 16, 29, 33). Even if HBV were related to ICC, it is not likely that HBV infection could be increasing ICC rates as HBV infection rates have declined, rather than increased, in the U.S. population (35).

It is not clear what other factors may be related to the increasing incidence of ICC among older Americans. In high-rate ICC areas, such as parts of Thailand, the dominant ICC risk factor is infestation with the liver flukes, *Clonorchis sinensis* and *Opisthorchis viverrini* (7). In low-risk ICC areas, such as the U.S., the major risk factor is preexisting primary sclerosing cholangitis, often seen in conjunction with inflammatory bowel disease (6). Although the incidence of primary sclerosing cholangitis does not seem to be increasing, survival may be, thus increasing the likelihood of developing ICC. Choledochal cysts and hepatolithiasis also increase the risk of ICC. Mutations in the hemochromatosis gene (*HFE*) and exposure to Thorotrast have each been associated with ICC, but the risks are not as great as they are for HCC (36, 37). It is also possible that diabetes increases the risk of ICC. A Danish cohort study reported an association between diabetes and PLC in Denmark (38). Although cholangiocarcinomas were included among the PLCs reported, it was not clear whether ICC, by itself, was significantly associated with diabetes. Further evaluation of the diabetes-ICC relationship will be required to clarify the relationship. ICC may also be diagnosed more frequently at the present time due to the growth, since the late 1970s, in the use of endoscopic retrograde cholangiopancreatography (Table 2) and/or because of liver transplantation. It is unlikely, however, that persons older than 70 years would be considered for a liver transplant, so the increasing incidence of ICC in persons 80 years and above is not entirely consistent with such an explanation.

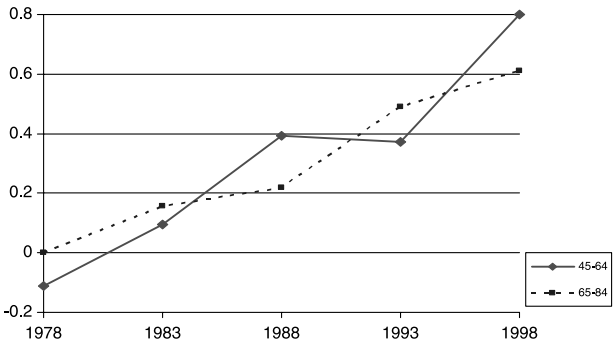

Figure 4. Calendar period effects on HCC. White males, 45 to 64 years old and 65 to 84 years old (SEER, 1976-1980 to 1996-2000).

[4] Personal communication, Dr. Gregory L. Armstrong, Division of Viral Hepatitis, Centers for Disease Control, Atlanta, GA.

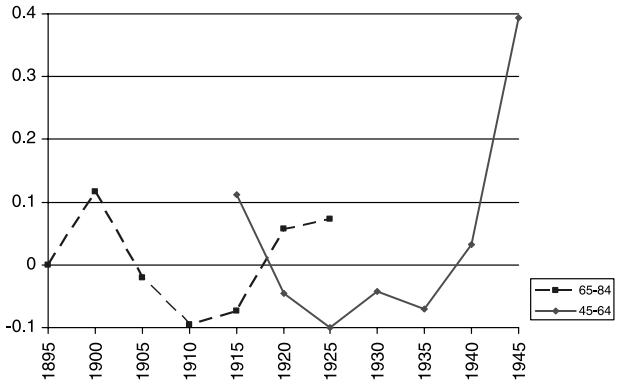

Figure 5. Cohort effects on HCC. White males, 45 to 64 years old and 65 to 84 years old (SEER, birth cohorts 1891-1900 and 1941-1950).

Although our study cannot directly examine the risk factors for either HCC or ICC, it could point to differences and similarities in the patterns of risk. The size and representativeness of the population are major strengths. There were several limitations however. Relatively small numbers of ICCs, particularly among Black men and women, suggest that the models of risk should be interpreted with caution. Another limitation was the inability to include individuals other than those classified as ''Black'' and ''White'' as the data for other populations were not available for the entire 25-year period. Finally, conclusions of age-period-cohort modeling that emphasize the youngest age groups should be accepted cautiously as there is inherent variability in birth cohort estimates based on younger people.

In summary, whereas rates of both HCC and ICC have increased, there are both similarities and differences in the patterns of risk. The patterns of risk of HCC among younger men suggest that particular attention should be paid to these groups in future studies. Case-control or cohort studies will be required to determine exactly which factors are most important in determining the risk of both tumors in the population.

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